

SDHB Pheochromocytoma and Paraganglioma Penetrance in a United States Population: An NIH Study

Kathryn S. King¹; Victoria Martucci¹; Robert Wesley²; Karen T. Adams¹; Margarita Raygada³; Constantine A. Stratakis⁴; Thanh-Truc Huynh¹; and Karel Pacak¹

¹Program in Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, USA.

²Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland 20892, USA.

³Section on Developmental Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, USA.

⁴Program in Developmental Endocrinology & Genetics (PDEGEN), Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), National Institutes of Health, Bethesda, Maryland, 20892 USA.

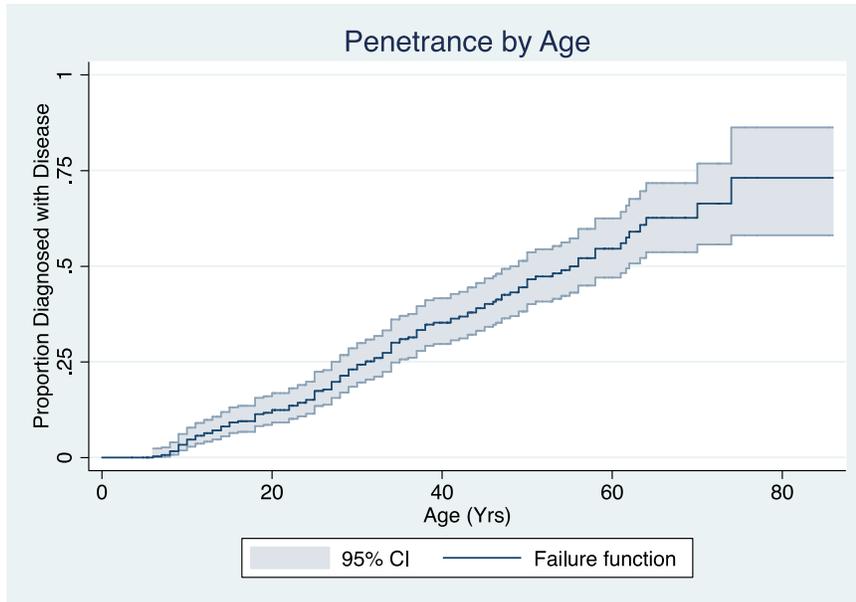
Background: Mutations within the B subunit of the succinate dehydrogenase complex are known to be associated with an aggressive pheochromocytoma/paraganglioma disease course, and many studies have been undertaken to describe the clinical presentation, biochemical phenotype, and potential therapeutic options for SDHB-related pheochromocytomas/paragangliomas.

Methods: A study on the penetrance of the SDHB gene linked to sex, age, and certain specific mutation types was conducted on 307 US patients, harboring 46 different mutations, who all underwent clinical screening with biochemical testing (plasma or urine catecholamines and/or metanephrines) and imaging with computed tomography (CT) or magnetic resonance imaging (MRI).

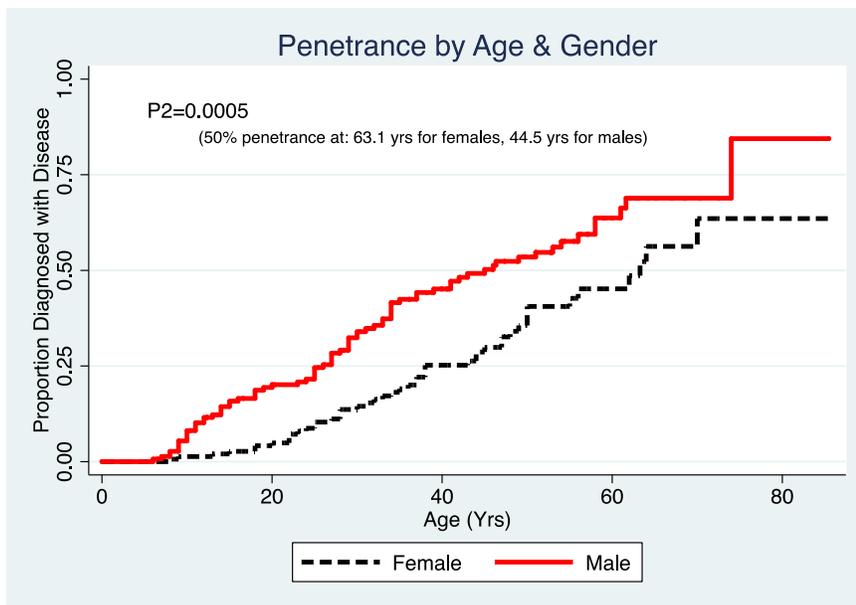
Results: Three hundred seven patients were screened for disease, of whom 124 had a diagnosis of pheochromocytoma/paraganglioma. Thus the overall penetrance of SDHB mutations in this patient population was found to be 40.4% (124 diseased/307 screened). A significant difference in penetrance between males and females was found: 50.7% (77/152) for males versus 30.3% (47/155) for females. Age-related penetrance analysis demonstrated a stratification of risk: three mutations (p.Ile127Ser, c.72+1G>T, p.Arg90X) had a slower rate of disease development (50% penetrance not achieved at 70 years and 62 years, respectively); patients with Exon 1 deletion demonstrated a faster rate of disease development (50% penetrance: 63.3 years); and patients with p.Val140Phe or p.Arg46X demonstrated the fastest rate of disease development (50% penetrance, both at 38 years).

Conclusions: Among this cohort of patients the overall penetrance was found to be 40.4%. We found a new striking difference in penetrance between males and females with males showing an earlier progression to disease: 50% penetrance at 44.5 years for males as compared to 63.1 years for females. However, the early onset of the disease in males was not found to be associated with accelerated fatal outcome. More studies are needed to determine the penetrance of SDHB mutations in other patient cohorts.

Figure 1: Kaplan-Meier Penetrance Curves. A) Overall age-related penetrance for 307 patients found to be positive for an SDHB mutation and screened for disease. The age at 50% penetrance for the group was found to be 55.92 years. B) Age-related penetrance separated by sex. The age at 50% penetrance for males was found to be 44.5 years and for females was found to be 63.1 years ($P = 0.0005$).



A



B